

Pacific University CommonKnowledge

School of Physician Assistant Studies

Theses, Dissertations and Capstone Projects

Summer 8-10-2013

The Effect of High-Altitude Therapy on Bronchial Hyperresponsiveness in Atopic Asthmatic Children

David Buchholz
buch2324@pacificu.edu

Follow this and additional works at: <http://commons.pacificu.edu/pa>

 Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Buchholz, David, "The Effect of High-Altitude Therapy on Bronchial Hyperresponsiveness in Atopic Asthmatic Children" (2013).
School of Physician Assistant Studies. Paper 427.

This Capstone Project is brought to you for free and open access by the Theses, Dissertations and Capstone Projects at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.

The Effect of High-Altitude Therapy on Bronchial Hyperresponsiveness in Atopic Asthmatic Children

Abstract

Background: Chronic asthma is a common, obstructive lung disease, affecting 300 million people worldwide. In the past 30 years prevalence has increased. Control of asthma is currently achieved with pharmacotherapeutic interventions such as inhaled sympathicomimetics and glucocorticocoids. High altitude climate therapy is an alternative method to pharmacological treatment. In the age before antibiotics, high altitude clinics in Europe were popular treatment destinations for those suffering from a variety of pulmonary disorders. Early 20th century researchers demonstrated appreciable benefits for asthmatics sojourning at high altitude. Despite a storied history, high altitude therapy is not a common therapy for refractory asthma in the modern era. Furthermore, the efficacy and underlying mechanism of high altitude therapy for the treatment of atopic asthma remains equivocal.

Method: The focus of this study was to review the contemporary literature (1992-2012) that focused on the efficacy of high altitude therapy for the treatment of bronchial hyperresponsiveness in atopic asthmatic children. An exhaustive search of Medline, CINAHL, and Web Of Knowledge was conducted with keyword “asthma” and “altitude”.

Results: In the four studies reviewed, there was a significant decrease in total eosinophil count, no improvement in methacholine provocation challenge, a significant improvement in histamine provocation challenge, a statistically significant decrease in CD4 lymphocyte activation, no change in total serum IgE, and weak evidence for improved lung function (FEV₁) in subjects undergoing high altitude therapy.

Conclusion: The current literature is thought provoking but lacking in quality, validity, and methodology. Furthermore, small sample sizes yield underpowered outcomes and statistically insignificant results. A large randomized controlled trial, with blinding of group allocation and outcome, is needed to further assess the efficacy of high altitude therapy for the treatment of asthma.

Keywords: *Asthma, high-altitude, bronchial hyperresponsiveness, bronchial hyperreactivity, airway inflammation.*

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

First Advisor

Rob Rosenow

Keywords

asthma, atopic, bronchial hyperresponsiveness, high altitude, therapy

Subject Categories

Medicine and Health Sciences

Rights

Terms of use for work posted in CommonKnowledge.

Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

The Effect of High-Altitude Therapy on Bronchial Hyperresponsiveness in Atopic Asthmatic Children

David Buchholz



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, 2013

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

BIOGRAPHY

[Redacted for privacy]

ABSTRACT

Background: Chronic asthma is a common, obstructive lung disease, affecting 300 million people worldwide. In the past 30 years prevalence has increased. Control of asthma is currently achieved with pharmacotherapeutic interventions such as inhaled sympathicomimetics and glucocorticocoids. High altitude climate therapy is an alternative method to pharmacological treatment. In the age before antibiotics, high altitude clinics in Europe were popular treatment destinations for those suffering from a variety of pulmonary disorders. Early 20th century researchers demonstrated appreciable benefits for asthmatics sojourning at high altitude. Despite a storied history, high altitude therapy is not a common therapy for refractory asthma in the modern era. Furthermore, the efficacy and underlying mechanism of high altitude therapy for the treatment of atopic asthma remains equivocal.

Method: The focus of this study was to review the contemporary literature (1992-2012) that focused on the efficacy of high altitude therapy for the treatment of bronchial hyperresponsiveness in atopic asthmatic children. An exhaustive search of Medline, CINAHL, and Web Of Knowledge was conducted with keyword “asthma” and “altitude”.

Results: In the four studies reviewed, there was a significant decrease in total eosinophil count, no improvement in methacholine provocation challenge, a significant improvement in histamine provocation challenge, a statistically significant decrease in CD4 lymphocyte activation, no change in total serum IgE, and weak evidence for improved lung function (FEV₁) in subjects undergoing high altitude therapy.

Conclusion: The current literature is thought provoking but lacking in quality, validity, and methodology. Furthermore, small sample sizes yield underpowered outcomes and statistically insignificant results. A large randomized controlled trial, with blinding of group allocation and outcome, is needed to further assess the efficacy of high altitude therapy for the treatment of asthma.

Keywords: *Asthma, high-altitude, bronchial hyperresponsiveness, bronchial hyperreactivity, airway inflammation.*

Acknowledgements

To my family for their support

To Torril for shelter from the storm

Table of Contents

Biography	2
Abstract	3
Acknowledgements	4
Table of Contents	5
List of Tables	6
List of Abbreviations.....	6
Background.....	7
Method	11
Results	11
Discussion.....	17
Conclusion.....	21
References	23
Tables.....	24

List of Tables

Table I: Summary of Findings

Table II: GRADE Quality Assessment

List of Abbreviations

ADR – Adverse drug reaction

BHR - Bronchial hyperresponsiveness/Bronchial hyperreactivity

Dpt - *Dermatophagoides pteronyssius*

FEV₁ – Forced Expiratory Volume in 1 second

HDM – House Dust Mite

LABA – Long-acting beta agonist

PEF – Peak expiratory flow

PC₂₀FEV₁ provocation concentration of histamine

PC₂₀FEV₁ provocation concentration of methacholine

SABA – Short-acting beta agonist

ICS – Inhaled corticosteroid

OCS – Oral corticosteroid

RV/TLC – Ratio of residual volume to total lung capacity

RCT – Randomized Controlled Trial

The Effect of High-Altitude Therapy on Bronchial Hyperresponsiveness in Atopic Asthmatic Children

BACKGROUND

Asthma affects 300 million people worldwide, making it one of the most common chronic diseases globally. The prevalence has risen over the past 30 year with currently 10-12% of adults and 15% of children affected by the disease.¹

Asthma is classified as an obstructive lung disease, caused by a narrowing of the upper airway due to bronchoconstriction, mucous plugs, and goblet cell metaplasia. Chronic inflammation leads to airway remodeling secondary to infiltration by inflammatory cells, whose ubiquitous and persistent presence cause changes in the “size, organization, and composition” of cells in the bronchial airway.² Changes in the architecture of the reticular basement membrane, due to subepithelial collagen deposition, result in the obstructive characteristics of asthma, as indicated by decreased forced expiratory volume in one second (FEV₁), and peak expiratory flow (PEF)¹. Acutely, exacerbation from allergens and other unknown etiologies, results in bronchial hyperreactivity (BHR), manifested clinically by wheezing, chest tightness, and dyspnea.

These acute symptoms of asthma are due to a variety of inflammatory cells including eosinophils, neutrophils, mast cells, dendritic cells, and T lymphocytes, with no predominant cell type wholly responsible¹. Triggers of asthma exacerbation may include infection, air pollution, allergens (pet dander, house dust mites (HDM), grass, tree pollen, and any other substances that lead to sensitization via protease activity), although acute

BHR has also been triggered by exercise, cold air, and hypoxia¹. While the etiology of asthma remains equivocal, it is accurate to define asthma as a multifactorial disease with complex interplay between genetic and environmental factors¹.

In regards to measurable outcomes, a review of the current literature suggests that the most relevant biomarkers of asthma severity and inflammation are total IgE levels, eosinophil counts, and blood T lymphocyte activation. The most relevant markers of lung function in asthmatics are FEV₁ and provocation concentration challenges (PC₂₀FEV₁). The markers of inflammation typically require more invasive diagnostic methods such as sputum smears and blood draws. For the purpose of diagnosing and controlling asthma, clinicians will usually defer to the less invasive tests of lung function (FEV₁, PEF). However, in the context of a research setting, markers of inflammation are routinely followed, as these provide further insight into the immunological etiology of asthma.

FEV₁ assesses overall lung function, provocation challenges measure the reactivity of the airway and, consequently, BHR. These are both commonly used clinical tools reflecting the degree of BHR and lung function. Invasive measures such as eosinophil count, serum IgE, and T-cell activation require blood draws and are not commonly used in clinical setting as a diagnostic or monitoring tool. However, the aforementioned serve as important biomarkers for the systemic immunological response to antigens, and are likely linked to asthma severity. CD4⁺ T cells are involved in the initiation and dissemination of inflammatory cytokines responsible for the systemic nature of asthma³. Peripheral eosinophil counts positively correlate with clinical severity of asthma⁴.

The current assortment of asthma medications is plentiful but may essentially be divided into two categories: bronchodilators aimed at relaxing bronchial smooth muscle and controller therapies aimed at reducing local airway and systemic inflammation. All asthmatics are initially equipped with a short-acting β_2 agonist inhaler. The β_2 agonist is intended to relax bronchial smooth muscle, and therefore, prevent bronchoconstriction in the setting of an acute attack. For long-term control of inflammation, an inhaler corticosteroid (ICS) is prescribed. The mode of action for ICS is to decrease inflammatory proteins (cytokines, adhesion molecules, inflammatory enzymes), and reduce airway mucosa infiltration by eosinophils, lymphocytes, and mast cells. The current approach for the treatment of asthma using ICS and β_2 agonists has proven effective in the majority of patients¹. In those patients with refractory asthma, asthma not responsive to pharmacotherapy, or asthmatics who experience significant adverse drug reactions (ADR) with systemic corticosteroids, alternative treatment methods have been investigated. One such treatment is high altitude therapy.

High-altitude therapy for pulmonary diseases has been around for more than a century. In the age before antibiotics, altitude therapy was a popular treatment for tuberculosis. Consumptives and asthmatics alike, sought refuge in the crisp mountain air and soft alpen-glow. In a 2011 narrative review by Rijssenbeek-Nouwens and Bel, Swiss and German researchers of the early 20th century reported that 68% of all asthmatics going to high-altitude clinics in Davos, Switzerland became free of asthma attacks within 2 to 3 days⁵.

Well into the 20th century researchers continued to examine the protective effects of high-altitude on asthma severity in both uncontrolled and controlled studies. In search of the underlying mechanism, many researchers now agree that avoidance of house dust mites (HDM) plays a central role in the reduction of airway hyperreactivity in asthmatics. At higher altitudes, low relative humidity creates an environment inhospitable for the mite. In one study, dust from houses in high-altitude mountains contained fewer HDMs and less allergens than house dust from sea level⁶.

A large case study by Konstantinos et al (2001) found that the prevalence of asthma in children living at 800-1200 meters was lower than the occurrence of asthma in their lowland peers (0-500 meters). Furthermore, children with asthma who lived in the mountains had fewer school absences per year, and fewer nights with dyspnea per year⁷. This study suggests that there is a link between altitude and asthma prevalence, and furthermore, that childhood bronchial asthma is less severe in children living at altitude.

A recent study by Karagiannidis et al (2006) demonstrated the beneficial effects of high-altitude therapy in both allergic and intrinsic (nonatopic) asthmatics. These intriguing findings suggest that there may be more to high-altitude therapy than simple avoidance of HDM, with the authors concluding that “factors other than allergen avoidance such as high UV light exposure, low endotoxin load or the dry air contribute to the beneficial influence of high-altitude climate therapy on asthma”.⁸

The degree of efficacy and true underlying mechanism of altitude therapy for the treatment of asthma remains largely unresolved. The purpose of this paper is to review the

contemporary literature in an attempt to answer the question, “What is the effect of high-altitude therapy on airway hyper-responsiveness in asthmatics?”

METHODS

An exhaustive search of the current literature was conducted using CINAHL, Medline/OVID, and Web of Science using the terms “asthma” and “altitude.” Additionally, bibliographies of included studies and a narrative review were cross-referenced for relevant articles. Search criteria was defined as all English-text articles published since 1993, that investigated the effects of high-altitude climate therapy on airway hyperresponsiveness in asthmatics. Inclusion criteria were that the study had to be a randomized controlled trial (RCT), and that the study investigated the effects of high altitude on atopic asthmatic children. Exclusion criteria were non-English articles, studies that examined the effects of extreme altitude therapy (>2000 meters), articles published before 1993, studies that investigated non-atopic asthmatics, and articles in the form of an editorial, letter to the editor, or narrative review.

RESULTS

Using the search terms “asthma” and “altitude” in a focused search with English-only articles and a publication window of 1993-2012, 49 articles were identified on Ovid-Medline. Of these, all abstracts were screened, and 6 were selected. Of these, 2 were excluded because they examined the effects of altitude above 5000 meters. One record was excluded because it the study groups included adults and non-atopic asthmatics. CINAHL

returned 37 records for “asthma” and “altitude” as text in title, duplicates were removed and one article was included. Web of Science turned up no additional articles that met inclusion criteria, or weren’t already included from previous searches. A total of four relevant articles are included in this systematic review. All included studies are RCTs published since 1993, where patients serve as their own controls, with the exception of Christie et al (1995)¹¹, which divides patients into control and experimental groups. All included studies involve altitude therapy at elevations between 1560 meters and 1,756 meters above sea level.

Peroni et al (1994)⁹ studied the effects of high altitude therapy and allergen avoidance on asthmatic children with HDM allergies. The researchers published the results of two separate trials, with similar methodologies, in a single paper. Both studies were conducted at the same location and lasted 9 months.⁹

The first study lasted from October through June and involved 22 atopic asthmatic children (mean age 10.6) during their residency at Il Istituto Pio XII in the Italian Alps (1756 meters). During this study a methacholine provocation challenge was given in October within 10 days of admission, again in January after 3 months of therapy, and in June at the completion of the study (at 9 months). Total serum IgE was also recorded during these study days. Peroni et al⁹ found that total serum IgE fell from 886 IU/mL to 463 IU/mL after 9 months of treatment, although the large standard deviation suggests no effect. Likewise, the preliminary results of the methacholine challenge suggest an improvement in BHR after 9 months of therapy, however the large standard deviation implies no effect.⁹

The following year, the researchers conducted a second study involving 23 atopic asthmatic children with (+) HDM. This study was conducted at the same Italian clinic. The median age was 10.8. The evaluations were performed in October upon entry to the clinic, again in March after 6 months of treatment, and in June after 9 months of treatment. In this study children were evaluated for bronchial hyperreactivity by provocation with a histamine challenge ($PC_{20}FEV_1$), followed a day later by HDM provocation ($DptPC_{20}FEV_1$); 2 days after the dust mite challenge the histamine challenge was repeated. BHR, as measured by the provocation concentration of histamine (before Dpt challenge), improved from 128.8 $\mu\text{g}/\text{ml}$ to 275.4 $\mu\text{g}/\text{ml}$ after 9 months of treatment ($P < 0.05$).⁹

To determine the effects of high-altitude climate therapy on BHR, peripheral T lymphocyte activation, and eosinophilia, Simon et al (1994)¹⁰ conducted a controlled trial where 17 children with perennial asthma were consecutively randomized although 3 were lost to followup, two due to infection and one due to lack of complete data. These subjects served as both the control and experimental group during a 5 week stay at a high altitude clinic in Davos (1560 meters). Patients were aged between 8 and 16 years old with a mean age of 12.5. There were 8 females and 6 males in the study. All patients had a diagnosis of unstable asthma, sensitivity to HDM, and no use of theophylline or oral steroids for at least 6 months prior.¹⁰

All children were on a β_2 agonist and “most used ICS as well”. Inhalation treatment was halted 12 hours prior to testing. All testing was done in the morning and included 9 separate respiratory function tests, including FEV_1 and PEF. Blood work was collected in heparinized tubes for measurement of IgE levels, leukocyte and lymphocyte subsets. Lung

function tests occurred on days 4, 23, and 37; Blood labs were collected on days 2, 21, and 35. A total of 14 children completed the study.¹⁰

Both absolute and relative numbers of peripheral eosinophils decreased significantly after 5 weeks of altitude therapy ($P<0.05$). The percentage of eosinophils expressed as a ratio of total leukocytes fell from 7.5% to just under 5% between days 2 and 35 of treatment ($P<0.05$). There was a decrease in CD25 expression on CD4+ cells, indicating a reduction in T lymphocyte activation markers. There was also an increase in naïve CD45RA+ T cells within the CD4+ cell population during the treatment course. Although it does not reach significance, the ratio of naïve T cells to antigen-experienced T cells increased in asthmatic subjects during 5 weeks of high altitude therapy.¹⁰

FEV₁ showed a statistically significant improvement after exercise, with FEV₁ % predicted increasing from 83% on Day 2 to 97% on Day 35 ($P<0.05$). PEF, another indicator of lung function, also improved. A decrease in residual volume/total lung capacity (RV/TLC) % predicted from 185% predicted to 168% suggests a decrease in pulmonary hyperinflation, a known sequela of chronic asthma. There was no change in total and specific IgE levels.¹⁰

Christie et al¹¹ examined the tendency for asthmatics residing at high-altitude to experience a deterioration in lung function, an increase in airway hyperresponsiveness, and an increase in urinary leukotriene excretion, upon return to lower altitude. 14 mild asthmatic children residing at the Netherlands Asthma Center (Davos, Switzerland) for at least 1 month were chosen to participate in a randomized controlled trial. Skin prick tests revealed that all children were positive for HDM extracts. All children were on albuterol,

all but two children were on ICS, two children were on cromoglycate, and one child was on nedocromil. Medication was not altered during the study.¹¹

In a “prospective, randomized fashion”, subjects were divided into two groups. One group returned to the Netherlands (360 meters above sea level) for a period of 14 days while the other group remained in Davos (1560 meters above sea level). All labs were conducted on two separate study days at the same time of day. In Davos, the study days were separated by 3 weeks; in the Netherlands group Study Day 1 was within 48 hours of departure and Study Day 2 within 48 hours of returning to Davos. Blood was drawn each study day for IgE and eosinophil count, and within one hour the histamine challenge and FEV₁ was performed. Two subjects in the control group were still included in the study despite refusing blood work on Study Day 2. Three measurements of FEV₁ were made during each test day and the mean value recorded.

Known prognostic factors included age, sex, atopy, % predicted FEV₁, and medications. Baseline FEV₁ % predicted, and age were similar between groups (mean 97.5%; 14.3). All children were atopic. The Davos group consisted of 4 males and 2 females; the Netherlands group consisted of 4 males and 4 females. All subjects in Davos managed their asthma with albuterol and an ICS. Subjects in the Netherlands had a more eclectic array of asthma medications, with all subjects on albuterol/ICS, plus two children on cromoglycate and one on nedocromil.

In the experimental group (Netherlands), there was a significant decrease in FEV₁ upon return to Davos, from 3.0 liters to 2.8 liters (P=0.04). In the control group (subjects

remaining in Davos), FEV₁ remained constant at 2.9 liters, and there was no change between study days.¹¹

Baseline levels for PC₂₀FEV₁ histamine challenge were similar between groups. Upon returning to Davos, the experimental group had a significant drop in PC₂₀FEV₁ from 1.7 mg/ml to 0.9 mg/ml (P=0.04). The children who remained in Davos had no significant difference in PC₂₀FEV₁, which remained at 1.5 mg/ml between study days (P=0.89).¹¹

The results of the study show that atopic asthmatic children who returned to the Netherlands experienced a decline in lung function as indicated by FEV₁ and an increase in BHR as indicated by PC₂₀FEV₁ histamine challenge. Those children remaining aloft in their high-altitude sojourn experienced no such decline in lung function or BHR.¹¹

Van Velzen et al (1996)¹² conducted a RCT of 16 atopic, asthmatic children to determine the effect of high-altitude on lung function, airway hyperresponsiveness, blood eosinophils, and serum IgE during a one month stay at a high-altitude asthma clinic. All children came from the Netherlands and were admitted to the Dutch Asthmacentre between September 1993 and March 1994 (Davos, 1560 meters). All subjects had been managing their asthma with “anti-inflammatory and bronchodilator drugs”, and these medications were continued at the same dosage throughout the study. Patients ranged between 10 and 18 years of age, with a median age of 14. There were 10 females and 6 males. FEV₁ % predicted was 94.2. All subjects were positive for HDM.¹²

Blood tests and lung function tests were conducted the second day and one month after arrival. PC₂₀methacholine challenge was conducted two days and one month after

arrival. Before the challenge long-acting beta agonist (LABA) and short-acting beta agonist (SABA) medications were withheld for 24 hours and 6 hours, respectively.

All 16 patients completed the study. FEV₁ showed no improvement over baseline. No improvement in bronchial hyperreactivity to methacholine challenge was observed, although an improvement in the adenosine monophosphate (AMP) provocation challenge, another indicator of airway hyperreactivity, was observed; A significant decrease in AMP responsiveness from 6.21 mg/ml at the start of the study to 25.78 mg/ml after one month of high altitude therapy suggests improvement in BHR. No change in serum IgE was observed. There was a reduction in total blood eosinophils from a mean of 372 per mm³ to 233 mm³ (P<0.01).¹²

DISCUSSION

These studies investigate the effect of altitude therapy on atopic asthmatic children. The results of lung function tests, provocation challenges, and immunological markers, are surrogate endpoints for asthma exacerbation, as defined by bronchial obstruction and hyperresponsiveness. While several studies uncovered statistically meaningful results, small sample size and lack of blinding were ubiquitous limitations. Furthermore, with the exception of Christie et al¹¹ researchers conducted their studies with the same subjects serving in both control and experimental groups; researchers studied the same subjects at two different altitudes, comparing baseline biomarkers to post-intervention biomarkers.

Three studies^{10,11,12} examined the effect of altitude on lung function, as measured by FEV₁. Christie et al[#] found a mean 0.2 liter decrease in FEV₁ in subjects who returned to sea

level from their high-altitude sojourn ($P=0.04$). This compares to patients who remained in Davos and experienced no alteration in FEV_1 ($P=0.35$). The small sample size for both groups is 5 children, suggesting indirectness via underpowered outcomes. Simon et al# finds an improvement in FEV_1 among 14 children remaining at high altitude for 5 weeks, although the P value is outside a level of significance ($P>0.05$). Van Velzen et al# finds a slight improvement in FEV_1 that is not statistically significant. With only one study showing an improvement in lung function, these results indicate there is as yet, insufficient evidence to conclude that FEV_1 improves with altitude therapy.

PC_{20} FEV_1 methacholine challenge was conducted by Peroni et al. and Van Velzen et al. to determine the effect of altitude therapy on BHR. Peroni found an improvement in PC_{20} FEV_1 among patients remaining in therapy for 9 months. These findings are statistically significant, yet due to the small sample size the standard deviation for both baseline PC_{20} FEV_1 and 9 month PC_{20} FEV_1 was very large, indicating areas of no effect. Van Velzen's PC_{20} FEV_1 methacholine challenge results were deemed to be "not statistically relevant" in the discussion section of that study. The results of the methacholine provocation challenge are not statistically relevant.

PC_{20} FEV_1 histamine challenge was addressed by Christie et al and Peroni et al.## P.E. Christie et al finds a significant decrease from baseline in patients returning to the Netherlands, from 1.7mg/ml to 0.9 mg/ml ($P=0.04$). These results are significant. Subjects remaining in Davos experienced no significant difference in PC_{20} FEV_1 histamine ($P=0.89$). Peroni et al found that the provocation concentration of histamine did improve in 23 atopic asthmatic children during a 9 month stay at high altitude, from 129 μ g/ml to 275 μ g/ml.

Both the P value (<0.05) and SD indicate a meaningful effect, although the sample size is small. In light of these limitations, both P.E. Christie and Peroni are able to show a statistically significant improvement in histamine provocation challenge among children exposed to high altitude therapy.

Total eosinophil counts were assessed by P.E. Christie and Simon et al. P.E. Christie et al found no significant change in total IgE levels or eosinophil counts in subjects returning to the Netherlands (sea level). Simon et al found a reduction in eosinophils over a 35 day period with statistical significance ($P<0.05$). Unfortunately, Simon et al does not include a quantitative value for the peripheral eosinophil count in this study and data must be inferred from a chart.

Total serum IgE levels were investigated by Peroni et al and Van Velzen et al. Peroni found that serum IgE levels decreased in 23 children from a mean of 886 to 463 IU/ml during a 9 month stay at high-altitude ($P<0.05$). The large SD indicates no effect. Van Velzen et al found no significant change in total IgE levels during 1 month of high-altitude therapy.

T cell activation before and after high altitude therapy in atopic asthmatics was studied by Simon et al using IL-2 receptor expression (CD25) on CD4⁺ and CD8⁺ lymphocytes, and CD45RA isoform expression in CD4⁺ T cells. Simon et al found a decrease in CD25 expression on CD4 T cells during a 5 week stay at high altitude. The quantitative data was not included in the results of that paper. Simon also found an increase in the ratio of naïve CD45RA⁺ T cells to memory CD45RO⁺ T cells within the CD4⁺

cell population that was statistically significant ($P < 0.05$). The quantitative values were not listed in the results.#

Quality of evidence was assessed using the GRADE system, which begins with an analysis of the quality of the evidence based on set criteria, and concludes with a judgment regarding the strength of recommendation (high, moderate, or weak). Quality of evidence was analyzed by outcome across studies. As summarized by outcome, the quality of evidence was very low in every case (see Table II). Every outcome category suffered from very serious limitations of methodology including lack of allocation concealment, lack of blinding, and same subjects serving as both control/experimental groups. Every outcome suffered from serious imprecision due to small sample size, and indirectness due to underpowered outcomes of interest. Outcomes such as T-cell activation, serum IgE, FEV₁, and eosinophil count also suffered from serious indirectness of evidence, as these are surrogate endpoints for BHR. A detailed analysis of the evidence, listed by outcome, is described below.

Two of the studies used the same group of children for control and experimental groups, a design by which lung function values were recorded before and after treatment exposure as evidence for comparison. This represents a limitation of methodology. Simon et al also remarks that “most children were on ICS” but does not elucidate how many children were on ICS, nor the type of ICS they were on. Since medication dosages were not altered during the study this caveat wouldn’t affect prognostic factors, however, a more in-depth analysis of baseline characteristics is expected. The length of treatment exposure among studies varied widely. Van Velzen et al studied the effects of altitude therapy for 1

month, Simon et al for 5 weeks, and P.E. Christie et al for 3 weeks for the control and 2 weeks for the experimental group. The difference in length of treatment introduces a level of inconsistency in the degree of exposure each group received. These inconsistencies reduce the quality of the evidence, as analyzed by the GRADE criteria.

CONCLUSION

Asthma is a multifactorial, complex, and prevalent disease. Currently the most widely accepted treatment for asthma is sympathicomimetic inhalers and/or oral/inhaled corticosteroids. While high-altitude treatment for chronic pulmonary disorders such as asthma has been around for over 100 years, the efficacy of this intervention has not been systematically proven in modern studies. Most studies are RCTs but lack validity due to a small sample size. Furthermore, a standardized quantitative method for determining asthma severity remains elusive. The lack of a specific biological marker for asthmatic severity persists in the failure of the medical community to agree upon a definition and etiology of this disease. The purpose of this paper was to define an array of biomarkers that are widely accepted as de facto sources for bronchial hyper-responsiveness, and, to systematically review all the relevant contemporary literature to determine the effect of high altitude on the indicators of BHR. The current literature is thought provoking but lacking in quality, validity, and methodology. Summarized by outcome across studies, the quality of evidence for each outcome was very low as determined by the GRADE system. A large randomized controlled trial, with blinding of group allocation and outcome, is needed to further assess the efficacy of high altitude therapy for the treatment of asthma.

References

1. Dan L. Longo, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, J. Larry Jameson, Joseph Loscalzo, Eds. Asthma. In: Peter J. Barnes, ed. *Harrison's principles of internal medicine online*. Vol Chapter 254. 18e ed. United States: McGraw-Hill Companies, Inc.; 2012.
2. Scheer, Amy, "Inhaled Corticosteroids and Their Affect on Reticular Basement Membrane Thickening in Patients with Asthma" (2009). *School of Physician Assistant Studies*. Paper 146. <http://commons.pacificu.edu/pa/146>
3. Kuipers H, Lambrecht B. The interplay of dendritic cells, Th2 cells and regulatory T cells in asthma. *Current Opinion In Immunology* [serial online]. December 2004;16(6):702-708.
4. Frette C, Annesi I, Korobaef M, Neukirch F, Dore M, Kauffmann F. Blood eosinophilia and FEV1. Cross-sectional and longitudinal analyses. *The American Review Of Respiratory Disease* [serial online]. May 1991;143(5 Pt 1):987-992
5. Rijssenbeek-Nouwens LH, Bel EH. High-altitude treatment: A therapeutic option for patients with severe, refractory asthma? *Clin Exp Allergy*. 2011;41(6):775-782.
6. Spiekma F, Zuidema P, Leupen M. High altitude and house-dust mites. *British Medical Journal* [serial online]. January 9, 1971;1(5740):82-84.
7. Gourgoulis K, Brelas N, Hatziparasides G, Papayianni M, Molyvdas P. The influence of altitude in bronchial asthma. *Archives Of Medical Research* [serial online]. September 2001;32(5):429-431.
8. Karagiannidis C, Hense G, Schmidt-Weber C, et al. High-Altitude Climate Therapy Reduces Local Airway Inflammation and Modulates Lymphocyte Activation. *Scandinavian Journal Of Immunology* [serial online]. April 2006;63(4):304-310.
9. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. 1994;149(6):1442-1446.
10. Simon HU, Grotzer M, Nikolaizik WH, Blaser K, Schoni MH. High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. *Pediatr Pulmonol*. 1994;17(5):304-311.
11. Christie PE, Yntema JL, Tagari P, Ysselstijn H, Ford-Hutchinson AW, Lee TH. Effect of altitude on urinary leukotriene (LT) E4 excretion and airway responsiveness to histamine in children with atopic asthma. *Eur Respir J*. 1995;8(3):357-363.
12. Van Velzen E, van den Bos JW, Benckhuijsen JA, van Essel T, de Bruijn R, Aalbers R. Effect of allergen avoidance at high altitude on direct and indirect bronchial hyperresponsiveness and markers of inflammation in children with allergic asthma. *Thorax*. 1996;51(6):582-584.

Summary of Findings (Table I)

Outcome	Study	# patients	Results	p-value	Quality
Total eosinophil count	P.E. Christie	14	0.109 x 10 ⁶ increase in eosinophils in subjects returning to Davos. 0.109 x 10 ⁶ decrease in eosinophils in subjects remaining in Davos.	none	Very low
	Simon	14	0.2 x 10 ⁶ reduction in eosinophils over 35 day period**	<0.05	
FEV ₁	P.E. Christie	14	0.2 liter decrease in FEV ₁ among subjects returning to the Netherlands. No change in FEV ₁ among subjects remaining in Davos.	0.04; 0.35	Very low
	Simon	14	FEV ₁ (% pred.) increased from 95.1 to 104 between days 2 and 35 at high altitude.	>0.05	
	Van Velzen	16	FEV ₁ (% pred.) increased from 92.1 to 97.0	Not statistically relevant	
PC ₂₀ FEV ₁ methacholine challenge	Peroni	22	Provocation concentration of methacholine increased from 124 µg/ml (±213) to 589 µg/ml (±664) after 9 months of high altitude therapy	<0.001	Very low
	Van Velzen	16	Provocation concentration of methacholine increased from 480 µg/ml to 620 µg/ml after 1 month of high altitude therapy.	Not statistically relevant	
PC ₂₀ FEV ₁ histamine challenge	Peroni	23*	Provocation concentration of histamine increased from 128.8 µg/ml (±30.5) to 275.4 µg/ml (±34.3)	<0.05	Very low
	P.E. Christie	14	PC ₂₀ FEV ₁ histamine decreased from 1.7 mg/ml to 0.9 mg/ml in subjects returning to the Netherlands. PC ₂₀ FEV ₁ histamine remained unchanged (1.5 mg/ml) in subjects remaining in Davos.	Netherlands (p=0.04); Davos (p=0.89)	
T-cell (CD4+) activation	Simon	14	Expression of the IL-2 receptor α chain in the CD4 + T cell population decreased from approximately 5% at baseline, to approximately 3.5% following 35 days of high altitude therapy.**	<0.05	Very low
Total serum IgE	Peroni	22	Total IgE serum levels decreased from 886 (±800) to 463 (±350) following 9 months of high altitude therapy.	<0.001	Very low
	Van Velzen	16	No significant change seen in total IgE levels during therapy (961 kU/L to 957 kU/L)	n/a	

*indicates results of Peroni et al. 2nd study results

**Indicates an estimation based on subjective interpretation of study tables

GRADE Quality Assessment (Table II)									
# of studies	Design	Part.	Mean age	Altitude	Limitations	Inconsistency	Indirectness	Imprecision	Quality of Evidence
Eosinophil count									
2	RCT	28 allergic asthmatic children	12.5 (Simon). 14 experimental (P.E. Christie); 15 control (P.E. Christie)	1560 meters	Very serious. (Lack of blinding, allocation concealment, 3 children lost to follow-up.)	No serious inconsistency	Serious indirectness (the outcomes of interest are underpowered due to small sample size)	Very serious imprecision (few patients, no p-value given for one study)	Very Low
FEV ₁									
3	RCT	34 allergic asthmatic children	12.5 (Simon). 14 experimental (P.E. Christie); 15 control (P.E. Christie). 14.6 (Van Velzen)	1560 meters	Very serious. Lack of blinding, allocation concealment, 3 children lost to follow-up	No serious inconsistency	Serious indirectness (the outcomes of interest are underpowered due to small sample size)	Very serious imprecision (Results not statistically relevant, with the exception of P.E. Christie (P=0.04))	Very Low
PC ₂₀ FEV ₁ methacholine challenge									
2	RCT	48 allergic asthmatic children	14.6 (Van Velzen).	1560 meters (Van Velzen); 1756 meters (Peroni)	Very serious. Lack of blinding, allocation concealment.	No serious inconsistency	Serious indirectness (outcomes of interest are underpowered due to small sample size)	Very Serious. Large SEM includes "no effect" (Peroni); Van Velzen lacks statistical significance	Very Low
PC ₂₀ FEV ₁ histamine challenge									
2	RCT	37 allergic asthmatic children	14 experimental (P.E. Christie); 15 control (P.E. Christie)	1560 meters (P.E. Christie); 1756 meters (Peroni)	Very serious. Lack of blinding, allocation concealment	No serious inconsistency	Serious indirectness (the outcomes of interest are underpowered due to small sample size)	Serious. Control group (P.E. Christie shows p=0.89)	Very Low

T-cell (CD4+) activation									
1	RCT	14 allergic asthmatic children	12.5 (simon);	1560 meters	Very serious. Lack of blinding, allocation concealment	No serious inconsistency	Serious. (outcomes of interest are underpowered.)	No serious imprecision	Very Low
Total Serum IgE									
2	RCT	48 allergic asthmatic children	14.6 (Van Velzen)	1560 meters (Van Velzen); 1656 meters (Peroni)	Very serious. Lack of blinding, allocation concealment	No serious inconsistency	Serious indirectness (the outcomes of interest are underpowered due to small sample size)	Large SEM includes “no effect” (Peroni); Van Velzen lacks statistical significance	Very Low